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1 **Interventions involving a major dietary component improve cognitive function in**
2 **cognitively healthy adults: a systematic review and meta-analysis.**

3

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24 **Abbreviations**

25 CVD; Cardiovascular disease

26 CAIDE; (Cardiovascular Risk Factors, Aging, and Incidence of Dementia) Dementia Risk Score

27 DASH; Dietary Approaches to Stop Hypertension

28 MedDiet; Mediterranean Diet

29 MMSE; Mini-Mental State Examination

30 3MS; Modified Mini-Mental Score

31 RCT; Randomized Controlled Trial

32 SMD; Standardized Mean Difference

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47 **Abstract**

48 Accumulating evidence suggests a role for diet in promoting brain health. The purpose of this
49 systematic review was to (i) quantitatively assess whether interventions with a major dietary
50 component can enhance cognition in cognitively healthy adults, and, (ii) identify responsive
51 domains of cognition to inform the design of future dietary trials. Electronic databases were
52 systematically searched to find eligible randomized controlled trials that assessed the effect of
53 interventions with a major dietary component on cognitive function or incident dementia, in
54 adults without known cognitive impairment. Standardized mean differences (SMD) (95%
55 confidence Interval [CI]) were combined using a random-effects meta-analysis and tests of
56 homogeneity of variance were calculated. Two trials reported dementia outcomes and were
57 qualitatively described. Fifteen trials encompassing 6,480 participants were eligible for meta-
58 analysis. Compared to control, intervention improved performance on measures of global
59 cognition (SMD=0.14; 95% CI 0.01 to 0.27, P=0.05; I^2 76%), executive function (SMD=0.11;
60 95% CI 0.04 to 0.18, P=0.003; I^2 0%) and processing speed (SMD=0.12; 95% CI 0.05 to 0.19,
61 P=0.001; I^2 0%). There was no effect of intervention on delayed memory (SMD=0.04; 95% CI -
62 0.02 to 0.09, P=0.18; I^2 4%). Significant heterogeneity and funnel plot asymmetry were detected
63 for global cognition but removal of studies with high risk of bias did not change the pooled
64 findings. Current evidence is limited but indicates that diverse interventions improve non-
65 memory cognitive functions during normal cognitive aging. Measures of executive function and
66 processing speed should be considered as feasible end-points in future dietary intervention trials.

67

68 Keywords: Randomized controlled trial; diet; cognitive function; dementia; meta-analysis

69

70 **1. Introduction**

71 Dementia is a global public health concern [1] due to increasing prevalence, high morbidity and
72 rising socioeconomic burden [1,2]. Addressing modifiable risk factors is likely to be among the
73 most promising way to reduce the number of future dementia cases [1-4] and considerable
74 research efforts are being made to identify safe and effective interventions to protect against age-
75 related neurodegeneration.

76

77 Accumulating evidence supports a role for diet on cognitive function and dementia risk.

78 Epidemiological studies have shown a positive link between high quality dietary patterns (for
79 example Mediterranean (MedDiet) and Dietary Approach to Stop Hypertension (DASH) diets)
80 and better cognitive functioning [5-6], slower rate of cognitive decline [7-8] and reduced risk of
81 dementia [8-10]. However, study findings have not been entirely consistent, largely because of
82 heterogeneity in study populations, diet assessment and cognitive outcomes [11-12] and no firm
83 dietary recommendations for brain health are available. Furthermore, causal relationships are
84 difficult to discern from observational data.

85

86 Randomized controlled trials (RCTs) are considered the gold standard for evaluating causal
87 associations. However, for prevention trials a major challenge is the identification of clinically
88 relevant end-points that are responsive to modification of risk factors, particularly in individuals
89 considered cognitively healthy or at early stages of neurodegeneration [13]. In the past few years,
90 data from RCTs evaluating dietary interventions on cognitive outcomes have emerged. However,
91 interventions have been extremely diverse and include diets such as the MedDiet, DASH,
92 calorie-restricted and low carbohydrate, either alone, or delivered simultaneously with other

93 factors, such as physical activity and/or treatment of vascular risks. Due to the limited number of
94 studies conducted to date and the diverse nature of interventions, as well as differences in study
95 populations, length of follow-up and the range of cognitive outcomes assessed, it is difficult for
96 investigators to draw firm conclusions on the consistency of observed effects. Therefore, we
97 aimed to systematically review available RCT data to assess the effect of interventions with a
98 major dietary component, on domains of cognitive function and dementia risk in adults without
99 known cognitive impairment. A secondary aim was to identify cognitive domain end-points most
100 responsive to the interventions, as this will inform the design of future trials in this important
101 research field.

102

103 **2. Approach**

104 This review was conducted according to recommendations in the PRISMA statement [14] and
105 the protocol was registered with PROSPERO: CRD42017057070.

106

107 **2.1 Search strategy and selection criteria**

108 We conducted an electronic search using MEDLINE, Embase and PsycINFO databases for
109 studies published through to 1st March 2018. A combination of MeSH and search terms were
110 used to identify studies that included: ‘diet*’, ‘dietary pattern’, ‘nutrition’, ‘food’, ‘nutrient’,
111 ‘weight loss*’, ‘life style*’, ‘cognition*’, ‘cognitive function’, ‘cognitive decline’, ‘cognitive
112 impairment’, ‘dementia’, ‘Alzheimer’s disease’. The primary search was limited to adults \geq 18
113 years and English language publications. We also examined citation lists of retrieved articles for
114 potential studies not identified by the electronic search.

115

116 Two reviewers (CME, YL) independently assessed studies for eligibility for inclusion based on
117 pre-defined criteria. We defined ‘dietary intervention’ as any intervention that targeted
118 modification of diet as a major component. Studies were considered eligible if they: (i) were
119 RCT design, (ii) evaluated the effect of dietary intervention in comparison to a control arm
120 receiving an active intervention or no active intervention; (iii) were conducted in a population
121 aged ≥ 18 years without known cognitive impairment; (iv) had an intervention period ≥ 3
122 months; (v) included a sample size ≥ 30 ; and (vi) reported outcomes of incident dementia (and
123 subtypes) or cognitive function measured using valid neuropsychological tests.

124

125 We excluded non-randomized trials, cohort studies, or interventions that assessed the effect of
126 nutrition supplements rather than dietary behavior, for example, macronutrient, vitamin or
127 mineral supplements. We excluded trials conducted in populations with neurological conditions
128 that could affect cognitive function such as Parkinson’s disease, mild cognitive impairment,
129 traumatic brain injury, depression or stroke. Duplicate articles from the same study examining
130 similar end-points were also excluded. Disagreements between reviewers regarding study
131 eligibility were resolved by discussion with a third reviewer (KY).

132

133 **2.2 Data extraction**

134 Two reviewers (CME, YL) extracted data from full text articles using a standard template to
135 summarize: sample size, population characteristics, intervention description, control/comparator
136 description, duration of follow-up, cognitive tests, study outcome(s) and post-intervention effect
137 estimates for intervention and control groups that included risk estimates for dementia outcome
138 (for example, Hazard Ratio [HR]) and means for cognitive outcomes, along with corresponding

139 measures of dispersion, for example SDs, or 95% CIs. For studies that examined composite
140 cognitive outcomes, the effect sizes for composite measure(s) were extracted as well as
141 individual neuropsychological test results where possible.

142

143 The primary outcomes were dementia incidence and cognitive function. To allow cognitive
144 function outcomes to be combined in a meta-analysis, the validated neuropsychological tests
145 reported in individual studies were examined by an expert neuropsychologist (ARK) who
146 classified them into cognitive domains according to standard theory as shown in Table A.1. This
147 process resulted in four cognitive domain categories that were utilized for meta-analysis. These
148 were; *global cognitive function* [which included tests to assess multiple aspects of cognition
149 including orientation, language and memory as well as cognitive composites that summarized
150 performance across a battery of neuropsychological measures], *executive function* [which
151 included tests of mental flexibility and problem solving], *processing speed* [which included tests
152 of ability to perform cognitive tasks quickly] and *delayed memory* [retention, recall and
153 recognition of previously presented information]. For each domain, validated cognitive test
154 scores or composite test scores that were reported consistently across studies were examined in
155 the meta-analysis as shown in Table 1.

156

157 **2.3 Assessment of study quality**

158 The internal validity of eligible trials was assessed by two independent reviewers (YL, GP) using
159 the Cochrane risk of bias tool [15]. Reviewers graded risk of bias across six potential sources:
160 selection, performance, detection, attrition, reporting, and other sources. For each study, overall
161 risk of bias was assessed as low (low graded bias across at least five categories), moderate (low

162 graded bias across at least four categories) or high (low graded bias in less than four categories).

163

164 **2.4 Statistical Analyses**

165 Incident dementia was reported in two trials [16,17] therefore, findings were qualitatively

166 described. To quantify the effect of diet interventions on cognitive function in cognitively

167 healthy adults, we calculated between-group standardized mean difference (SMD) and 95%

168 confidence intervals (95% CI) at follow-up for each of the cognitive domains and then pooled

169 results using a random-effects meta-analysis [18] to take account of heterogeneity between and

170 within included trials. SMDs of ≤ 0.2 , >0.5 and <0.8 , and >0.8 were considered small, moderate,

171 and large effects, respectively [19]. Where necessary, we used standard formulae to convert the

172 reported effect estimates from individual studies into SMD (95% CI). For studies with more than

173 one active treatment group, we included the most intensive intervention in the meta-analysis or

174 where similarly intensive interventions were evaluated (e.g. MedDiet supplemented with olive

175 oil or nuts) we considered the alternate intervention in sensitivity analyses. Where multivariate

176 analyses were presented by the authors, we calculated SMD adjusted for confounders in the final

177 reported model.

178

179 Study heterogeneity was assessed using both Cochran's Q-statistic ($P < 0.05$) and the *I*-squared

180 (I^2) statistic. We considered an I^2 value greater than 50% indicative of high heterogeneity [20].

181 Evidence of publication bias was assessed by examining funnel plot asymmetry and by Begg and

182 Egger tests [21]. In cases of high heterogeneity, we repeated the pooled analysis after removing

183 studies assessed as high risk of bias. All statistical analyses were performed using Review

184 Manager Software (Review Manager, Version 5.3, Copenhagen: The Nordic Cochrane Centre,

185 The Cochrane Collaboration, Denmark).

186

187 **3. Results**

188 **3.1 Study characteristics**

189 The PRISMA flowchart for eligible studies is shown in Figure 1. The primary search yielded
190 1,615 original titles of which 1,589 were excluded after title and abstract screen. One additional
191 article [22] was identified from a citation search within identified articles. Full texts of 27 studies
192 were independently assessed by two reviewers and 12 were excluded (Figure 1). Fifteen RCTs
193 met the inclusion criteria [16, 17, 22-34] as shown in Table 1.

194

195 Most trials (n = 7) were conducted in Europe (Spain, Netherlands, Germany, Italy and Finland),
196 followed by Australia (n = 3), USA (n = 3), Canada (n = 1) and Korea (n = 1). Two studies
197 involved participants from different PREDIMED study centers (Barcelona [33] and Navarra [17,
198 28]) and were considered as separate studies. Furthermore, authors from the PREDIMED-
199 Navarra center reported independent end-points of interest in two articles [17, 28] and to avoid
200 duplication, we included only the cognitive outcomes shown in Table 1 for each of these articles.
201 All studies involved both males and females, eight were conducted exclusively in older adults (\geq
202 60 years) [16,17,22,27,29,30,31,33], one in adults \geq 50 years [34]. Two trials were conducted in
203 individuals at high Cardiovascular disease (CVD) risk [17,33] one in individuals at increased
204 dementia risk (CAIDE \geq 6) [31], two in people with type 2 diabetes [25,26], two in obese adults
205 [23,30] and one in hypertensive adults [32]. The length of follow-up ranged from 3 months to 8
206 years. Five trials were nested in larger RCTs [17,25,26,28,32,33] and three of these did not
207 include a baseline cognitive function measurement [25,26,28].

208 Cognitive outcomes from 15 RCTs were pooled in meta-analyses; ten trials reported outcome
209 measures of global cognitive function and processing speed and nine trials reported measures of
210 executive function and delayed memory.

211
212 Each trial was assessed for risk of bias. Two trials were considered low [16,31], seven were
213 considered moderate [17,22,26-28,30,32,33] and five were considered high [23-25,29,34] risk of
214 bias as shown in Figure 6.

215

216 **3.2 Effect of intervention on incident dementia**

217 Dementia incidence was reported in two RCTs [16,17]. The PreDIVA trial [16] involving 3,526
218 older adults, assessed the effectiveness of a multi-domain intervention to optimize diet, physical
219 activity, smoking, weight and blood pressure, compared to usual primary care, on dementia
220 incidence. After 6.7 years, dementia occurred in 121 (7%) of the intervention group and 112
221 (7%) of the control group, with no significant intervention effect on all-cause dementia (HR
222 0.92, 95% CI 0.71-1.19; P = 0.54) or Alzheimer's disease (HR 1.05, 95% CI 0.78-1.41; P =
223 0.74). Secondary analyses indicated significant beneficial effects on all-cause dementia for
224 participants with hypertension (HR 0.54, 95% CI 0.32-0.92; P = 0.02) and those without pre-
225 existing CVD (HR 0.64, 95% CI 0.44-0.94; P = 0.02), who adhered more strictly to the
226 intervention. The PREDIMED-Navarra trial [17], reported fewer cases of dementia in the
227 MedDiet supplemented with olive oil (n = 12, 3%) or nuts (n = 6, 2%) intervention groups,
228 compared with a low-fat control group (n = 17, 5%) after 6.5 years of follow-up. However, risk
229 estimates were not reported given the small number of dementia cases observed in this study.

230

231 **3.3 Effect of intervention on cognitive function**

232 The pooled effect of interventions with a major diet component on cognitive domains is shown
233 in Figures 2-5 and described in more detail below.

234

235 **3.3.1 Global cognition**

236 Ten RCTs involving 6,057 participants (3,188 intervention and 2,869 control) reported global
237 cognitive function on a composite score [22,31, 32], MMSE [16,17,27,29,33] or the Modified
238 Mini-Mental score (3MS) [25,30]. Figure 2 shows the pooled analysis of all ten trials that
239 indicated a significant beneficial effect of intervention on global cognitive function (SMD =
240 0.14; 95% CI 0.01, 0.27, P = 0.03) compared to control with high between study heterogeneity
241 (I^2 76%). A funnel plot showed potential asymmetry (not shown) with evidence of publication
242 bias (Begg's P = 0.03 and Egger's P = 0.02).

243

244 **3.3.2 Executive function**

245 Nine RCTs involving 2,830 participants (1,445 intervention and 1,385 control) reported
246 executive function on the Stroop interference [22-25,32], Trail Making Test B [28,30] or Color
247 Trail 2 [33]. One trial reported a composite executive function score that incorporated Stroop
248 interference and Trail B-A tests [31]. The combined analysis showed a small positive effect of
249 intervention versus control on executive function (SMD = 0.11; 95% CI 0.04, 0.18, P = 0.003; I^2
250 0%) shown in Figure 3.

251

252 **3.3.3 Processing speed**

253 Ten RCTs involving 3,037 participants (1,548 intervention and 1,489 control) reported

254 processing speed on the Trail Making Test A [17,25,26,30], Inspection time [23,24], Digit
255 Symbol Substitution [32], Color Trail 1 [33] or a composite processing speed score [22,31]. The
256 pooled analysis showed faster processing speed in response to intervention compared to control
257 (SMD = 0.12; 95% CI 0.05, 0.19, P = 0.001; I^2 0%) shown in Figure 4.

258

259 **3.3.4 Delayed memory**

260 Nine RCTs involving 5,690 participants (2,958 intervention and 2,732 control) reported delayed
261 memory on the Rey Auditory Verbal Learning Test [22,24-26,28,33], Visual Association [16],
262 Visual Paired Associates [32] or a composite memory score [31]. Figure 5 shows the pooled
263 analysis of the nine trials, which indicated no significant effect of intervention on delayed
264 memory (SMD = 0.04; 95% CI -0.02, 0.09, P = 0.18; I^2 4%).

265

266 **3.4 Sensitivity analysis**

267 For studies with two active treatment groups, the less intensive treatment was examined in the
268 sensitivity analysis. None of the less intensive treatments were more effective on the outcomes.
269 We performed a sensitivity analysis for global cognition by removing trials with high risk of bias
270 [23-25,29,34]. This attenuated the combined effect (SMD = 0.13 [95% CI, 0.04, 0.30], P = 0.13)
271 but heterogeneity remained high (I^2 79%, P < 0.001). We also removed two trials with the
272 shortest (3-4-month) follow-up time [32, 34] and this attenuated the effect for global cognition
273 (SMD 0.11 [95% CI, -0.02, 0.24], P=0.09) but had little effect on the pooled estimates for
274 executive function (SMD 0.10 [95% CI, -0.03, 0.18], P<0.01) or processing speed (SMD 0.12
275 [95% CI, 0.05, 0.20], P<0.001).

276

277 **4. Discussion**

278 This is one of the first meta-analysis examining the effect of interventions with a major diet
279 component on cognitive outcomes in adults without known cognitive impairment. Results from
280 one large trial [16], showed no overall effect of a multicomponent intervention on dementia after
281 6.7 years, but a significantly lower risk for those with greatest adherence to the intervention. In
282 terms of cognitive function, the pooled analysis of available data showed positive effects of
283 intervention on global cognition, executive function and processing speed but no effect on
284 delayed memory. In all cases, pooled effect sizes were small (SMD 0.1 to 0.2).

285
286 Cognitive function declines progressively during normal aging with high variability in the rate of
287 decline, particularly in older age [35]. Processing speed and executive function appear to decline
288 earlier and, to a greater extent, than other cognitive domains [36] and impairment in these
289 abilities can interfere with other complex processes, such as memory and behavior and adversely
290 affect the ability to perform everyday tasks [37-39]. Therefore, interventions to improve
291 processing speed and executive function may be an effective means to counter the
292 pathophysiological brain changes leading to cognitive decline during aging. Our pooled results
293 show that interventions with a major dietary component improve these cognitive abilities in non-
294 demented adults and are particularly public health relevant, given the longer life expectancy of
295 populations worldwide, and the anticipated rapid increase in the number of people affected by
296 cognitive impairment.

297
298 We did not observe a pooled effect of intervention on delayed memory. This may be partly
299 explained by a "ceiling effect" for detection of diet-induced improvement in memory among

300 cognitively healthy adults. In experimental studies, reduction in energy and fat appear to improve
301 long-term memory function in obese adults [40] and recent clinical data has shown improved
302 memory function in response to diet-induced weight loss in obese patients with cognitive
303 impairment [41]. Therefore, those at high risk of memory impairment may benefit most from
304 dietary modification and further clinical trials in vulnerable populations are warranted. It also
305 remains possible that diet has protective effects on other aspects of memory such as visuospatial
306 memory that were not fully investigated in this meta-analysis.

307

308 Several plausible biologic pathways support a role for diet in optimizing brain health. Diet has
309 important anti-oxidant and anti-inflammatory properties that can reduce both oxidative stress and
310 inflammation implicated in the pathogenesis of cognitive decline and dementia.

311 Experimental studies have shown direct effects of diet on neuronal cell signaling [42], neuronal
312 membrane integrity [43] and inflammation [44] and diet can have an indirect impact on brain
313 health by modulating cardio-metabolic risk. Compelling evidence from several clinical trials
314 have demonstrated significant reductions in cardiometabolic risk in response to diet intervention,
315 even in the absence of weight loss [45,46]. Processing speed and executive function are
316 adversely affected by hypertension, atherosclerosis and cardiovascular disease [47,48].

317 Therefore, it is possible that the observed benefit of dietary intervention on these cognitive
318 abilities is mediated by improved cardiometabolic health. However, further mechanistic evidence
319 is needed to explain how diet influences cognition and dementia. Incorporation of neuroimaging
320 biomarkers in future studies could provide greater insight into potential mechanisms of diet on
321 brain health. Preclinical changes in brain structure precede cognitive decline and can predict
322 dementia risk [49]. Evidence supporting a protective role for high quality diets on MRI-measured

323 brain structure in middle-age [50] and older adults [51] is beginning to emerge but require
324 prospective confirmation in larger populations.

325

326 Several limitations should be considered in interpreting findings from this meta-analysis. First,
327 included trials were highly diverse in the nature (composition, dose, delivery and duration) of
328 intervention evaluated. For example, interventions ranged from single food group to whole diet
329 interventions to multicomponent interventions that targeted diet as well as other lifestyle
330 behaviors and cognitive training. Hence, it is not possible to determine the effects attributable to
331 diet on cognitive performance. There were too few dietary interventions to allow meaningful
332 meta-analysis across cognitive domains, however, the effects observed were generally stronger
333 for the multicomponent trials. For the dietary trials, follow-up ranged from 3 months to 6 years
334 and most of these studies were considered poor quality. Therefore, from the data currently
335 available, it is not possible to define optimal dietary strategies to enhance cognitive function, nor
336 the optimal duration of intervention. Additional high-quality trials that are well designed and
337 focus solely on diet intervention for cognitive health are required. Second, while heterogeneity
338 was substantial across interventions, we attempted to minimize this for cognitive outcomes by
339 pooling results across standardized cognitive domains. Publication bias was not detected in most
340 pooled analyzes but substantial heterogeneity and publication bias was evident for global
341 cognition. In this case, removal of trials with high risk of bias did not improve overall
342 heterogeneity. Other potential differences between the studies include the global cognition
343 measures and populations studied, such as age, genetic risk and educational status, which may
344 account for some of the individual variation in response to intervention. Despite limitations, our
345 results are the most comprehensive effort to quantitatively synthesize the effectiveness of

346 interventions with a major dietary component for cognitive functioning in non-demented adults
347 and our findings have relevance for informing end-point measures for future dietary intervention
348 studies. We adhered to recommendations for conducting systematic reviews and performed an
349 objective assessment of the internal validity for included trials.

350

351 **5. Conclusions**

352 In summary, this review demonstrates small beneficial effects of interventions that include a
353 major dietary component on non-memory cognitive domains in adults without known cognitive
354 impairment. These small effects could potentially translate to a substantial improvement in
355 cognitive health if implemented at a population level. Our results indicate that change in
356 processing speed and executive function are feasible end-point measures in future diet
357 intervention trials.

358

359 **6. Future research to advance this area**

360 Further research is required to determine the precise nature of dietary modification to enhance
361 cognition in different populations and the duration of intervention needed for optimal effect.
362 Incorporation of neuro-imaging outcome measures could help to elucidate mechanisms of action
363 and identify subtle neurological diet-induced changes that may not be possible to detect with
364 standard cognitive tests. In addition, few diet intervention studies have incorporated clinical
365 dementia end-points therefore further well-designed RCTs are needed to comprehensively
366 investigate the effect of diet on dementia and subtypes of dementia.

367

368

369

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375
376

References

- [1] World Health Organization. Dementia: A public health priority, http://apps.who.int/iris/bitstream/10665/75263/1/9789241564458_eng.pdf?ua=1; 2012 [accessed 15 January 2018].
- [2] Alzheimer's Disease International. World Alzheimer Report : The Global impact of Dementia,<https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf>; 2015 [accessed 15 January 2018]
- [3] Barnes DE, Yaffe K. Projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol* 2011;10:819-28.
- [4] Deckers K, van Boxtel MP, Schiepers OJ, de Vugt M, Muñoz Sánchez JL, Anstey KJ, et al. Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. *Int J Geriatr Psychiatry* 2015;30:234-46.
- [5] McEvoy CT, Guyer H, Langa KM, Yaffe K. Neuroprotective Diets Are Associated with Better Cognitive Function: The Health and Retirement Study. *J Am Geriatr Soc* 2017;65:1857-62.
- [6] Wengreen H, Munger RG, Cutler A, Quach A, Bowles A, Corcoran C, et al. Prospective study of Dietary Approaches to Stop Hypertension- and Mediterranean-style dietary patterns and age-related cognitive change: the Cache County Study on Memory, Health and Aging. *Am J Clin Nutr* 2013;98:1263-71.

- [7] Tangney CC, Li H, Wang Y, Barnes L, Schneider JA, Bennett DA, et al. Relation of DASH- and Mediterranean-like dietary patterns to cognitive decline in older persons. *Neurology* 2014;83:1410-16.
- [8] van de Rest O, Berendsen AA, Haveman-Nies A, de Groot LC. Dietary patterns, cognitive decline, and dementia: a systematic review. *Adv Nutr* 2015 13;6:154-68.
- [9] Singh B, Parsaik AK, Mielke MM, Erwin PJ, Knopman DS, Petersen RC, et al. Association of mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis* 2014;39:271-82.
- [10] Lourida I, Soni M, Thompson-Coon J, Purandare N, Lang IA, Ukoumunne OC, et al. Mediterranean diet, cognitive function, and dementia: a systematic review. *Epidemiology* 2013;24:479–89.
- [11] Olsson E, Karlström B, Kilander L, Byberg L, Cederholm T, Sjögren P. Dietary patterns and cognitive dysfunction in a 12-year follow-up study of 70 year old men. *J Alzheimers Dis* 2015;43:109-19.
- [12] Samieri C, Grodstein F, Rosner BA, Kang JH, Cook NR, Manson JE, et al. Mediterranean diet and cognitive function in older age. *Epidemiology* 2013;24:490-99.
- [13] de Jager CA, Dye L, de Bruin EA, Butler L, Fletcher J, Lampaert DJ, et al. Criteria for validation and selection of cognitive tests for investigating the effects of foods and nutrients. *Nutr Rev*. 2014;72:162-79.
- [14] Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Ann Intern Med* 2009;151: 264-69.
- [15] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.

- [16] Moll van Charante EP, Richard E, Eurelings LS, van Dalen JW, Ligthart SA, van Bussel EF, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *Lancet* 2016;388:797-805.
- [17] Martínez-Lapiscina EH, Clavero P, Estruch R, Salas-Salvadó J, San Julián B, et al. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. *J Neurol Neurosurg Psychiatry* 2013;84:1318-25
- [18] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-88.
- [19] Cohen J. *Statistical Power Analysis for the Behavioral Sciences*, 2nd ed. New Jersey: Erlbaum; 1988.
- [20] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
- [21] Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001;54:1046-55.
- [22] Knight A, Bryan J, Wilson C, Hodgson JM, Davis CR, Murphy KJ. The Mediterranean Diet and Cognitive Function among Healthy Older Adults in a 6-Month Randomised Controlled Trial: The MedLey Study. *Nutrients* 2016;8. pii: E579.
- [23] Brinkworth GD, Buckley JD, Noakes M, Clifton PM, Wilson CJ. Long-term effects of a very low-carbohydrate diet and a low-fat diet on mood and cognitive function. *Arch Intern Med*. 2009;169:1873-80.
- [24] Crichton GE, Murphy KJ, Howe PR, Buckley JD, Bryan J. Dairy consumption and working memory performance in overweight and obese adults. *Appetite* 2012;59:34-40.
- [25] Espeland MA, Rapp SR, Bray GA, Houston DK, Johnson KC, Kitabchi AE, et al. Long-term impact of behavioral weight loss intervention on cognitive function. *J Gerontol A Biol Sci Med*

- Sci. 2014;69:1101-8.
- [26] Koekkoek PS, Ruis C, van den Donk M, Biessels GJ, Gorter KJ, Kappelle LJ, et al. Intensive multifactorial treatment and cognitive functioning in screen-detected type 2 diabetes-- the ADDITION-Netherlands study: a cluster-randomized trial. *J Neurol Sci.* 2012;314:71-7.
- [27] Lee KS, Lee Y, Back JH, Son SJ, Choi SH, Chung YK, et al. Effects of a multidomain lifestyle modification on cognitive function in older adults: an eighteen-month community-based cluster randomized controlled trial. *Psychother Psychosom.* 2014;83:270-78.
- [28] Martínez-Lapiscina EH, Clavero P, Toledo E, San Julián B, Sanchez-Tainta A, Corella D, et al. Virgin olive oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized trial. *J Nutr Health Aging* 2013;17:544-52.
- [29] Mazza E, Fava A, Ferro Y, Rotundo S, Romeo S, Bosco D, et al. Effect of the replacement of dietary vegetable oils with a low dose of extravirgin olive oil in the Mediterranean Diet on cognitive functions in the elderly. *J Transl Med* 2018;16:10. doi: 10.1186/s12967-018-1386-x.
- [30] Napoli N, Shah K, Waters DL, Sinacore DR, Qualls C, Villareal DT. Effect of weight loss, exercise, or both on cognition and quality of life in obese older adults. *Am J Clin Nutr* 2014;100:189-98.
- [31] Ngandu T, Lehtisalo J, Solomon A, Levälähti E, Ahtiluoto S, Antikainen R, et al. A 2-year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet* 2015;385:2255-63.
- [32] Smith PJ, Blumenthal JA, Babyak MA, Craighead L, Welsh-Bohmer KA, Browndyke JN, et al. Effects of the dietary approaches to stop hypertension diet, exercise, and caloric restriction on neurocognition in overweight adults with high blood pressure. *Hypertension* 2010;55:1331-38.
- [33] Valls-Pedret C, Sala-Vila A, Serra-Mir M, , Corella D, de la Torre R, Martínez-González MÁ, et

- al. Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial. *JAMA Intern Med* 2015;175:1094-103.
- [34] Witte AV, Fobker M, Gellner R, Knecht S, Flöel A. Caloric restriction improves memory in elderly humans. *Proc Natl Acad Sci U S A*. 2009;106:1255-60.
- [35] Blazer DG, Yaffe K, Karlawish J. Cognitive aging: a report from the Institute of Medicine. *JAMA* 2015;313:2121-22.
- [36] Baltes P. Theoretical propositions of life-span developmental psychology: On the dynamics between growth and decline. *Dev Psychol* 1987;23: 611–26.
- [37] Cahn-Weiner DA, Boyle PA, Malloy PF. Tests of executive function predict instrumental activities of daily living in community-dwelling older individuals. *Appl Neuropsychol* 2002;9:187-91.
- [38] Royall DR, Lauterbach EC, Kaufer D, Malloy P, Coburn KL, Black KJ. The cognitive correlates of functional status: a review from the Committee on Research of the American Neuropsychiatric Association. *J Neuropsychiatry Clin Neurosci* 2007;19:249-65.
- [39] Classon E, Fällman K, Wressle E, Marcusson J. Relations between Concurrent Longitudinal Changes in Cognition, Depressive Symptoms, Self-Rated Health and Everyday Function in Normally Aging Octogenarians. *PLoS One*. 2016;11:e0160742.
doi:10.1371/journal.pone.0160742.
- [40] Attuquayefio T, Stevenson RJ. A systematic review of longer-term dietary interventions on human cognitive function: Emerging patterns and future directions. *Appetite* 2015;95:554-70.
- [41] Horie NC, Serrao VT, Simon SS, Gascon MR, Dos Santos AX, Zambone MA, et al. Cognitive Effects of Intentional Weight Loss in Elderly Obese Individuals With Mild Cognitive Impairment. *J Clin Endocrinol Metab* 2016;101:1104-1112.

- [42] Dauncey MJ. New insights into nutrition and cognitive neuroscience. *Proc Nutr Soc.*2009;68:408-15.
- [43] Bourre JM. Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 2: macronutrients. *J Nutr Health Aging*2006;10:386-99.
- [44] Vauzour D, Camprubi-Robles M, Miquel-Kergoat S, Andres-Lacueva C, Bánáti D, Barberger-Gateau P, et al. Nutrition for the ageing brain: Towards evidence for an optimal diet. *Ageing Res Rev* 2017;35:222-40.
- [45] Esposito K, Maiorino MI, Petrizzo M, Bellastella G, Giugliano D. The effects of a Mediterranean diet on the need for diabetes drugs and remission of newly diagnosed type 2 diabetes: follow-up of a randomized trial. *Diabetes Care.* 2014;37:1824-30.
- [46] Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med.* 2013;368:1279-90.
- [47] Walker KA, Power MC, Gottesman RF. Defining the Relationship Between Hypertension, Cognitive Decline, and Dementia: a Review. *Curr Hypertens Rep* 2017;19:24. doi: 10.1007/s11906-017-0724-3.
- [48] Eggermont LH, de Boer K, Muller M, Jaschke AC, Kamp O, Scherder EJ. Cardiac disease and cognitive impairment: a systematic review. *Heart* 2012;98:1334-40.
- [49] Marsland AL, Gianaros PJ, Kuan DC, Sheu LK, Krajina K, Manuck SB. Brain morphology links systemic inflammation to cognitive function in midlife adults. *Brain Behav Immun.* 2015;48:195-204.
- [50] Mosconi L, Murray J, Tsui WH, Li Y, Davies M, Williams S, et al. Mediterranean Diet and Magnetic Resonance Imaging-Assessed Brain Atrophy in Cognitively Normal Individuals at Risk for Alzheimer's Disease. *J Prev Alzheimers Dis* 2014;1:23-32.

- [51] Gu Y, Brickman AM, Stern Y, Habeck CG, Razlighi QR, Luchsinger JA, et al. Mediterranean diet and brain structure in a multiethnic elderly cohort. *Neurology* 2015;85:1744-51.

Figure 1: PRISMA flow chart of the process used to select trials for inclusion in this systematic review and meta-analysis

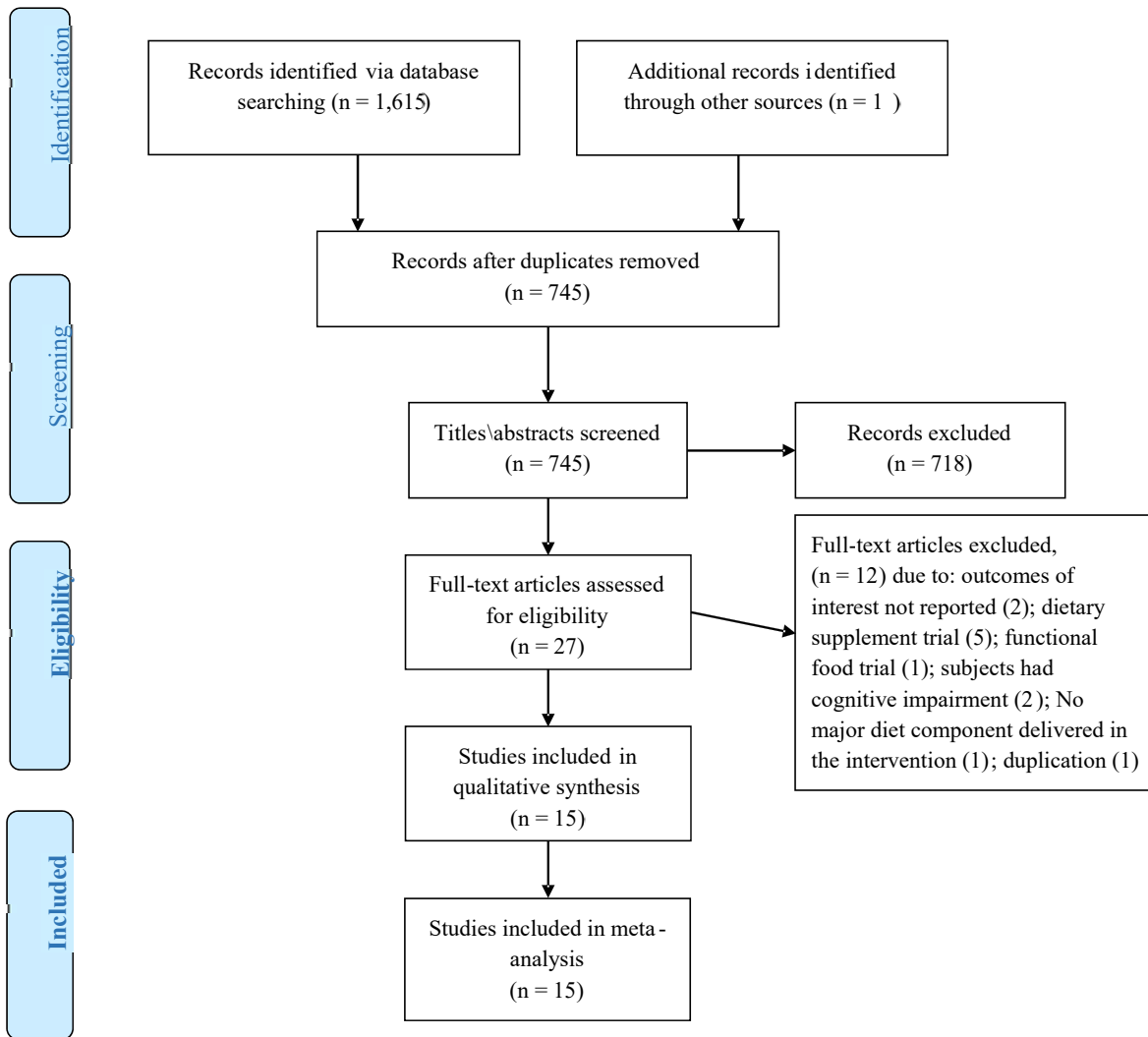


Figure 2. Forest plot showing the effect of intervention versus control on global function (n = 10)

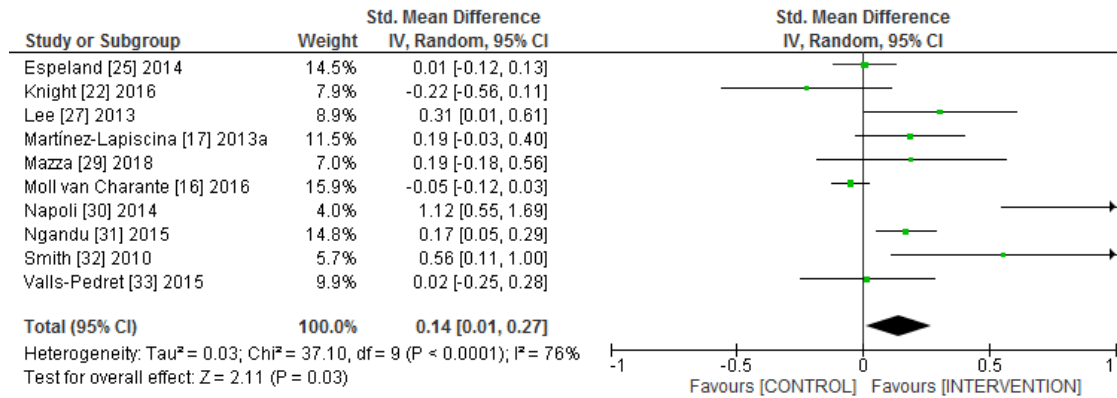


Figure 3. Forest plot showing the effect of intervention versus control on executive function (n = 9)

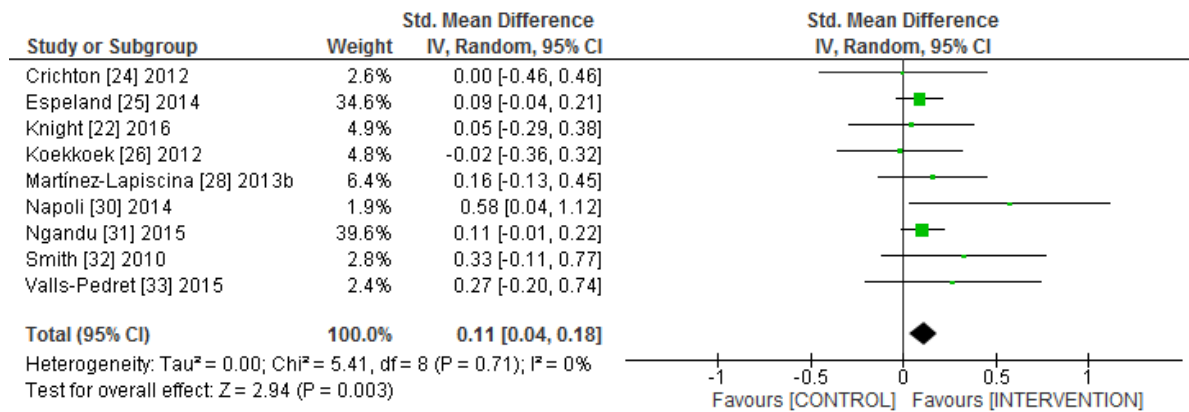


Figure 4. Forest plot showing the effect of intervention versus control on processing speed (n = 10)

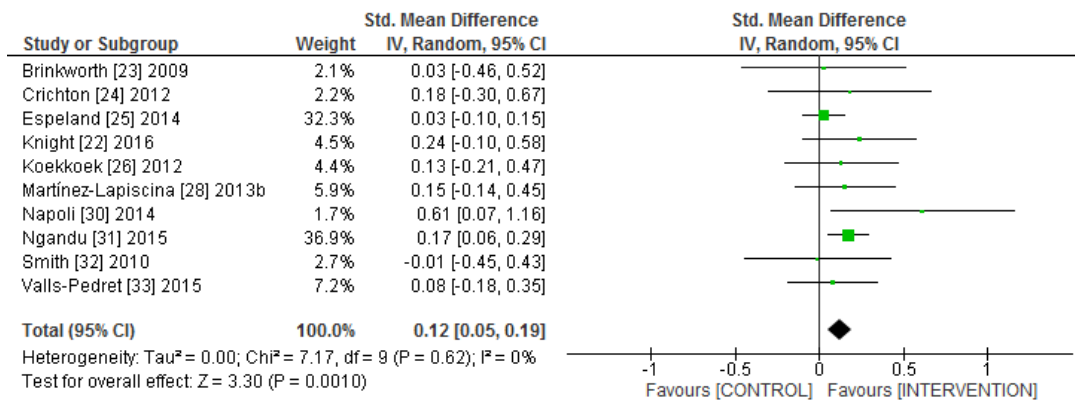


Figure 5. Forest plot showing the effect of intervention versus control on delayed memory (n = 9)

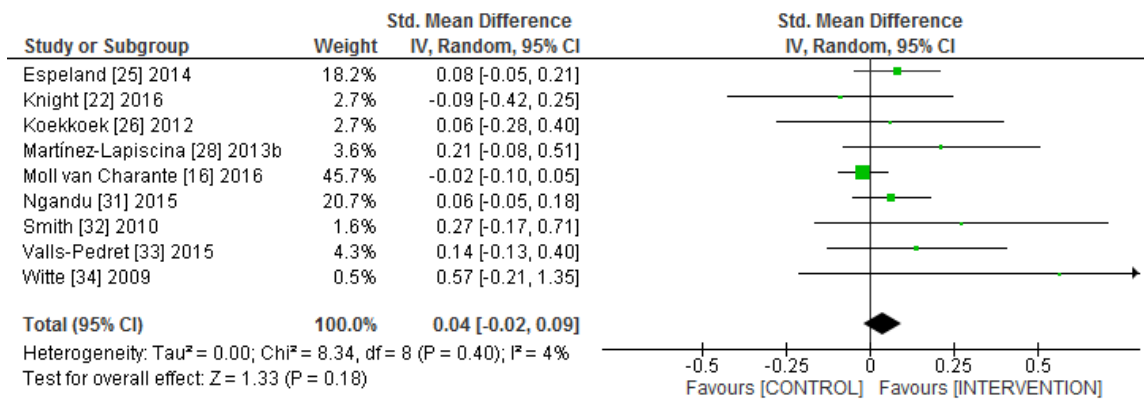


Figure 6: Summary of the risk of bias across six categories for the included studies in this systematic review and meta-analysis

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Brinkworth [23] 2009	?	?	?	+	+	?	+
Crichton [24] 2012	?	?	?	?	-	+	-
Espeland [25] 2014	?	?	?	+	+	-	+
Knight [22] 2016	+	+	+	+	?	?	+
Koekkoek [26] 2012	+	+	-	?	+	-	+
Lee [27] 2013	+	+	-	+	?	+	-
Martínez-Lapiscina [17] 2013a	+	+	+	+	-	-	+
Martínez-Lapiscina [28] 2013b	+	+	?	+	+	?	+
Mazza [29] 2018	?	?	?	?	-	+	+
Moll van Charante [16] 2016	+	+	?	+	+	+	+
Napoli [30] 2014	?	+	?	+	?	+	+
Ngandu [31] 2015	+	+	+	+	?	+	+
Smith [32] 2010	+	?	+	+	?	-	+
Valls-Pedret [33] 2015	+	+	-	+	-	+	-
Witte [34] 2009	-	?	?	?	?	+	+

Table 1: Characteristics of trials examining the effect of diet-based intervention on cognitive function or dementia incidence (n = 15)

Ref	County	Population	Age (years)	Sample size	Intervention	Control	Follow-up	Cognitive outcomes of interest				
								Dementia	Global function	Executive function	Processing speed	Delayed memory
23	Australia	Abdominally obese adults	24-64	118	Low Carbohydrate diet	Low Fat diet	12 mon	-	-	-	Inspection Time	-
24	Canada Australia	Healthy adults with BMI ≥ 25	18-75	59	High dairy diet	Low dairy diet	12 mon	-	-	Stroop	Inspection Time	RAVLT
25	USA	Type 2 diabetics	45-76	978	Diet and physical activity	Diabetes Structured Education	8 yr.	-	3MS	Stroop	TMT-A	RAVLT
22	Australia	Older adults	≥ 65	166	MedDiet	Habitual diet	6 mon	-	Mean z-score for 11 Modified Stroop cognitive tests		Mean z-score for symbol search and coding test	RAVLT
26	Netherlands	Type 2 Diabetics		258	Intensive lifestyle advice	Standard care	~3.2 yr.	-	-	Stroop	TMT-A	RAVLT
27	Korea	Older adults	≥ 60	460	Increased fruit and vegetable intake; 2 servings fish/wk.; physical activity 30min x 3/wk.	Standard care	18 mon	-	MMSE	-	-	-
17	Spain	Adults at high CVD risk	55-80	1055 max	1) MedDiet + Olive Oil 2) MedDiet + nuts	Low fat diet	6.5 yr.	Cases per group	MMSE	-	-	-
28	Spain	Adults at high CVD risk	55-80	271	1) MedDiet + Olive Oil 2) MedDiet + nuts	Low fat diet	6.5 yr.	-	-	TMT-B	TMT-A	RAVLT
29	Italy	Older adults with MMSE > 20	≥ 65 yr	110	MedDiet + Olive Oil	MedDiet	12 mon	-	MMSE			
16	Netherlands	Older adults	70-78	3526	Diet, physical activity, smoking cessation, weight and blood pressure management	Standard care	6.7 yr.	Dementia incidence	MMSE	-	-	VAT

Ref	County	Population	Age (years)	Sample size	Intervention	Control	Follow-up	Cognitive outcomes of interest				
								Dementia	Global function	Executive function	Processing speed	Delayed memory
30	USA	Obese older adults	≥ 65	107	1) Diet weight-management program 2) Exercise 3) Diet and exercise	General healthy diet information	12 mon	-	3MS	TMT-B	TMT-A	RAVLT
31	Finland	Older adults with CAIDE ≥6	60-77	1260	Intensive diet, exercise, cognitive training, vascular risk monitoring	Standard care - general health advice	2 yr.	-	Mean z-score for all 14 cognitive tests	Mean z- score for 5 cognitive tests	Mean z-score for 3 cognitive tests	Mean z- score for 4 cognitive tests
32	USA	Hypertensive overweight adults	52.3±9.6	124	1) DASH-diet alone (DASH-A), 2) DASH-weight management 3) DASH-weight management and exercise	Standard care	4 mon	-	Mean z-score for 5 cognitive tests	Stroop	DSST	VPA
33	Spain	Adults at high CVD risk	55-80	447	1) MedDiet + Olive Oil 2) MedDiet + nuts	Low fat diet	4.1 yr.	-	MMSE	Color Trail 2	Color Trail 1	RAVLT
34	Germany	Adults with MMSE ≥26	50-80	50	Calorie restricted diet	Habitual diet	3 mon	-	-	-	-	RAVLT

BMI= Body Mass Index; RAVLT = Rey Auditory Verbal Learning Test; HbA1c = Glycated haemoglobin; TMT-A = Trail Making Test A; MMSE = Mini-Mental State Examination; CVD = Cardiovascular disease; MedDiet = Mediterranean diet; TMT-B = Trail Making Test B; VAT – Visual Association Test; 3MS = Modified Mini-Mental State; CAIDE = Cardiovascular Risk Factors, Aging, and Incidence of Dementia; DASH = Dietary Approaches to Stop Hypertension; DSST = Digit Symbol Substitution Test

